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communication to Applicants, along with copies of the references cited. If there was no Form PTO-892, and the Office Action Summary was mistakenly marked in that regard, Applicants request that such a clarification be made in the next communication from the Examiner.

In Paper No. 8, the Examiner rejects claims 1- 19 under 35 U.S.C. §103(a), as being unpatentable over "Fizet (abstract of EP 610742)." (*See*, Paper No. 8, p. 3). Applicants submitted an Information Disclosure Statement in the instant application on December 14, 2001, and properly cited European Patent Application No. EP 610742 of Fizet, along with its English language equivalent, U.S. Pat. No. 5,487,817 of Fizet (herein after referred to as "Fizet"). For the sake of clarity, Applicants would like to point out that all references to "Fizet" made herein apply to the U.S. Patent, *e.g.*, column and line numbers thereof.

In making her rejection, the Examiner contends that Fizet discloses a process for recovering tocopherols and sterols from natural sources, and she argues that this disclosure somehow "embraces Applicant's [*sic*] claimed invention." (*See*, Paper No. 8, p. 3). The Examiner contends that Fizet discloses a process "for isolation of sterols" which includes (a) esterifying sterols with fatty acids, (b) distilling the resulting mixture to produce a residue of sterol esters, (c) cleaving the sterol esters to form free sterols and (d) isolating the sterols from the residue. The Examiner then contends that the instant claims differ from the prior art only in that they cite conditions for the reactions and classify the cleavage of the ester as transesterification. The Examiner then argues that there is in fact no transesterification, but only "the breaking of sterol ester to get free sterol." (*See*, Paper No. 8, p. 3). The Examiner then summarily argues that "[i]t would have been obvious to one skilled in the art at the time of invention to isolate sterols from the mixture by first transesterifying the mixture to for sterols esters and then separating other products by distillation or any other means and then cleaving the sterol to break the ester bond with sterol to get free sterol." (*See, id.* at pp.3-4).

On this basis, the Examiner concludes that the subject matter of the instant claims would have been obvious within the meaning of 35 U.S.C. §103(a).

Applicants strenuously traverse the Examiner's rejection, along with her contentions and arguments in support thereof for the following reasons.

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As the Examiner should be well aware of, prior to rendering an ultimate conclusion of obviousness during the examination of a U.S. utility patent application, the Examiner must first establish a *prima facie* case of obviousness, which Applicants may then rebut with argument and evidence, which may then be evaluated in making a final determination of obviousness. (M.P.E.P. §2142).

It is well-settled that in order to establish a *prima facie* case of obviousness based upon a single reference, and thus shift the burden of proving non-obviousness onto Applicants, the Examiner MUST satisfy each of the following three criteria: (1) the reference must contain a teaching or suggestion which would motivate one of ordinary skill in the art to modify the reference as suggested by the Examiner (it is not sufficient to say that the reference can be modified without a teaching in the cited reference to suggest the desirability of such a modification); (2) there must be a reasonable expectation of success; and (3) the reference must teach or suggest each and every element of Applicant's claimed invention. The teaching or suggestion to modify the cited art and the reasonable expectation of success must both be found in the prior art and not in Applicants' Specification. (M.P.E.P. §2143).

Before discussing the specific requirements for establishing *prima facie* obviousness, Applicants would like to highlight their claimed invention. Applicants' claimed invention is directed to a surprisingly economical and environmentally friendly process for producing sterols, wherein the process comprises two separate transesterification steps. (See, Applicants' Specification, page 2, lines 25-27). Applicants' claimed process comprises: (a) providing an oil distillation residue comprising sterol esters and partial glycerides; (b) transesterifying the partial glycerides with a lower alcohol in the presence of a basic catalyst under mild transesterification conditions to form fatty acid alkyl esters and glycerol; (c) removing excess lower alcohol, the basic catalyst, the glycerol and the fatty acid alkyl esters, to form a bottom product comprising the sterol esters; and (d) transesterifying the sterol esters at a temperature of from 90°C to 145°C and a pressure of from 2 to 10 bar for a period of from 4 to 10 hours to form free sterols.

Applicants would also like to reiterate that the reaction set forth in section (d) of claim 1 is in fact a transesterification, contrary to the Examiner's statements. As

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clearly claimed, and explained in the Specification, for example, at page 6, line 21, through page 7, line 21, the second transesterification reacts the sterol ester with an alcohol, whereby the acyl portion of the sterol ester is transferred to the alkoxy portion of the alcohol. This is transesterification. For the Examiner's convenience, Applicants have attached hereto as Exhibit A, a copy of selected pages from Hawley's Condensed Chemical Dictionary, 12th Ed. (1993), wherein "transesterification" is defined as "ester interchange", and "ester interchange" is defined as "[t]he reaction between an ester and another compound with exchange of alkoxy or acyl groups to form a different ester." (See, Lewis Sr., R. (Rvsd.), Hawley's Condensed Chemical Dictionary, 12th Ed., pp. 473 & 1163, Van Nostrand Reinhold Company, New York (1993)).

Applicants respectfully submit that Fizet does not disclose a process for isolating sterols from an oil distillation residue containing sterol esters and partial glycerides, wherein two separate transesterifications, under different conditions are carried out to attain economical and environmental advantages.

To begin with, Fizet discloses a process for recovering tocopherols and sterols from deodorizer sludges. The sterols present in the sludge are first esterified with fatty acids present in the sludge, *i.e.*, a direct esterification. This esterified sludge containing sterol fatty acid esters, fatty acids, tocopherols and various other components is then distilled twice to remove a first fraction containing fatty acids, and a second fraction containing tocopherols. (See, *e.g.*, Fizet, claim 1, subsection (b)). The residue remaining contains sterol fatty acid esters from which sterols may be obtained. Fizet discloses that the sterol fatty acid ester-containing residue also contains glycerides, other waxes, as well as numerous other substances. (See, col. 5, lines 46-53). Fizet discloses that sterols may be obtained from the residue via acid-catalyzed transesterification carried out in a steel autoclave over a period of from 1 to 5 hours. (See, *id.* at lines 53-64). This harsh, single transesterification step wherein glycerides, tocopherol esters, sterol esters and numerous other substances are all simultaneously transesterified is avoided by Applicants' claimed invention.

Applicants have discovered that sterols can be produced from oil distillation residues containing glycerides and sterol esters, more economically and in a manner friendlier to the environment, by first transesterifying the mixture under mild conditions such that the sterol

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esters remain substantially esterified and the glycerides are what is predominantly transesterified to produce fatty acid alkyl esters and glycerol which can then be removed, resulting in a concentrated sterol ester residue. This concentrated sterol ester residue is then treated in the second transesterification step under the more harsh conditions needed to transesterify the sterol esters.

Fizet clearly fails to teach or suggest each and every element of Applicants' claimed invention. First, Fizet does not teach or suggest the transesterification of an oil distillation residue containing sterol esters and partial glycerides under mild conditions whereby the sterol esters remain substantially bound as esters. Such a transesterification is not even suggested. Fizet clearly teaches the treatment of the sterol ester-containing residue via a single transesterification to obtain free sterols. The reference fails to suggest a two-step transesterification with an intervening separation of glycerol and other unwanted compounds from the sterol esters.

Moreover, Fizet contains no teaching or suggestion which would motivate one of ordinary skill in the art to modify Fizet as suggested by the Examiner in order to arrive at Applicants' claimed invention. Fizet does not teach or suggest subsequent treatment of the sterol ester-containing residue other than the single harsh transesterification. The residue is simply transesterified under normally harsh conditions whereby all substances are simultaneously transesterified, and subsequent purification, *e.g.*, via crystallization, is performed. Nothing in Fizet suggests the claimed two-step transesterification. Nor is there any suggestion that the sterol esters should be concentrated prior to final transesterification via Applicants' claimed mild transesterification and separation of glycerol, etc. Fizet clearly recognizes the presence of many other compounds in the sterol ester-containing residue.

Given the lack of any teaching or suggestion to modify the reference as suggested by the Examiner, and that fact that the reference otherwise fails to teach or suggest each and every element of the claimed invention, one of ordinary skill in the art would find no reasonable expectation of successfully achieving the claimed invention in the teachings of Fizet.

Accordingly, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness, as none of the three criteria necessary to establish a *prima facie* case


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of obviousness has been satisfied. Thus, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

In view of the remarks set forth above, Applicants submit that all pending claims patentably distinguish over the prior art of record and known to Applicants, either alone or in combination. Accordingly, reconsideration, withdrawal of the rejection and a Notice of Allowance for all pending claims are respectfully requested.

Respectfully submitted,

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(Date)

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Copy of Lewis Sr., R. (Rvsd.), Hawley's Condensed Chemical Dictionary, 12th Ed., pp. 473 & 1163, Van Nostrand Reinhold Company, New York (1993) (4 pages).

Hawley's
Condensed Chemical
Dictionary

TWELFTH EDITION

Revised by
Richard J. Lewis, Sr.



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See nicotinamide adenine dinucleotide phosphate.

TPO rubber. Abbreviation for thermoplastic polyolefin rubber.
See elastomer.

Tpp. (1) Abbreviation for triphenyl phosphate.
(2) Abbreviation for thiamine pyrophosphate.
See cocarboxylase.

TPT. (1) Abbreviation for triphenyltetrazolium chloride.
See tetrazolium chloride.
(2) Abbreviation for tetraisopropyl titanate.

trace element. (micronutrient). An element essential to plant and animal nutrition in trace concentration, i.e., minute fractions of 1% (1000 ppm or less). Plants require iron, copper, boron, zinc, manganese, potassium, molybdenum, sodium, and chlorine. Animals require iron, copper, iron, manganese, cobalt, selenium, and potassium. Such elements are also called micronutrients. Do not confuse with "tracer."

tracer. A chemical entity (almost invariably radioactive and usually an isotope) added to the reacting elements or compounds in a chemical process, which can be traced through the process by appropriate detection methods, e.g., Geiger counter. Compounds containing tracers are often said to be "tagged" or "labeled." Carbon-14 is a commonly used tracer and radioactive forms of iodine and sodium are also used. Many complex biochemical reactions have been examined in this way (e.g., photosynthesis). Non-radioactive deuterium (hydrogen isotope) is sometimes used, the detection being by molecular-weight determination. Radioactive enzymes are also available for tracer studies, e.g., ribonuclease, pepsin, trypsin, and others.
See also labeling (2).

trademark. (TM). A word, symbol, or insignia designating one or more proprietary products or the manufacturer of such products, which has been officially registered with the government trademark agency. The accepted designation is a superior capital R enclosed in a circle; however, quotation marks may also be used, as in this dictionary. The term "trade name," though widely used, is not applicable to such products; according to the U.S. Trademark Association, a trade name is the name under which a company does business, e.g., the Blank Chemical Company. Use of a trademark without proper indication of its proprietary nature places the name in jeopardy; a number of trademarks have been invalidated as a result of this practice.

trade name. See trademark.

trade sales. In the paint industry, this term is applied to paints intended for sales to the general public, as in hardware stores and similar outlets.

tragacanth gum. CAS: 9000-65-1.

Properties: Dull white, translucent plates or yellowish powder; soluble in alkaline solutions, aqueous hydrogen peroxide solution; strongly hydrophilic; insoluble in alcohol. Combustible. **Constituents:** Polysaccharides of galactose, fructose, xylose, and arabinose with glucuronic acid. **Occurrence:** Southwestern Europe, Greece, Turkey, Iran.

Grade: USP, FCC, No. 1, 2, 3.

Use: Pharmacy (emulsions), adhesives, leather dressing, textile printing and sizing, thickener and emulsifier, dyes, food products (ice cream, desserts), toothpastes, coating soap chips and powders, hair-wave preparations, confectionery, printing inks, tablet binder.

tranquilizer. See psychotropic drug

trans- See cis-

"Trans 1030" [Trans-Chemco]. TM for a series of additives.

Use: As silicone antifoams for sauna baths, rug shampoos, food processing, wastewater treatment, agricultural applications, and cutting oils.

transalkylation. A type of disproportionation reaction by which toluene is hydrogenated to benzene and mixed xylene isomers free from ethylbenzene, avoiding the formation of methane resulting from the conventional hydrodealkylation process. Transalkylation of toluene to benzene involves the use of a catalyst; the yield is claimed to be 97%, based on toluene feed.

transaminase. (aminopherase). An enzyme that facilitates the reversible transfer of an amino group from an α -amino acid to an α -keto acid.

transamination. The use of nitrogen of one amino acid for synthesizing another amino acid *in vivo*.

trans effect. Bond holding a group trans to the more electronegative or other labilizing group is weakened.

transesterification. See: Ester interchange.

transferase. An enzyme whose activity causes a transfer of a radical from one molecule to another. Examples are transaminases, transacetylases, and transmethylases, which effect

ESR. See spin resonance.

essential. (1) Containing the characteristic odor or flavor, (i.e., the essence) of the original flower or fruit: an essential oil, usually obtained by steam distillation of the flowers or leaves or cold-pressing of the skin. (2) As applied to certain amino acids, fatty acids, and vitamins, this term is used by biochemists to mean that the compound in question is a necessary nutritional factor that is not synthesized within the body of the animal and thus must be obtained from external sources. Eight amino acids are classified as essential on this basis.

See also amino acid.

essential oil. A volatile oil derived from the leaves, stem, flower, or twigs of plants, and usually carrying the odor or flavor of the plant. Chemically, they are often principally terpenes (hydrocarbons), but many other types also occur. Essential oils (except for those containing esters) are unsaponifiable. Some are nearly pure single compounds, as oil of wintergreen, which is methyl salicylate. Others are mixtures, as turpentine oil (pinene, dipentene), and oil of bitter almond (benzaldehyde, hydrocyanic acid). Some contain resins in solution and are called oleoresins or balsams.

Properties: Pungent taste and odor, usually nearly colorless when fresh but becoming darker and thick on exposure to the air; optically active, $d_{20}^{25} 0.850-1.100$; soluble in alcohol, carbon disulfide, carbon tetrachloride, chloroform, petroleum ether, and fatty oils; insoluble in water except for individual constituents of some oils which may be partially water-soluble, resulting in a loss of these constituents during steam distillation.

Derivation: (1) By steam distillation, (2) by pressing (fruit rinds), (3) by solvent extraction, (4) by maceration of the flowers and leaves in fat and treating the fat with a solvent, (5) by enfleurage.

Use: Perfumery, flavors, thinning precious-metal preparations used in decorating ceramic ware.

See also terpeneless oil and specific entries. Further information can be obtained from the Essential Oil Association of U.S.

Note: Many essential oils are now made synthetically for a wide variety of fragrances and flavoring agents. Use of these synthetics is increasing because of a shortage of natural products.

ester. An organic compound corresponding in structure to a salt in inorganic chemistry. Esters are considered as derived from acids by the exchange of the replaceable hydrogen of the latter for an organic radical. The usual reaction is that of an acid (organic or inorganic) with an alcohol or other organic compound rich in OH groups.

Esters of acetic acid are called acetates, and esters of carbonic acid carbonates. See also fatty ester.

ester gum. Hard, semisynthetic resin produced by esterification of natural resins (especially rosin) with polyhydric alcohols (principally glycerol but also pentaerythritol). Flash p 375F (190C). Combustible. Grade: By color, also as gum rosin or wood rosin. Use: Paints, varnishes, and cellulosic lacquers.

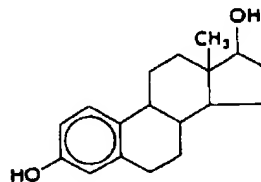
esterification. The process of producing an ester by reaction of an alcohol with an acid.

ester interchange. (transesterification; interification). The reaction between an ester and another compound with exchange of alkoxy or acyl groups to form a different ester.

ester number. (1) The number of milligrams of alkali necessary for saponification of the glyceryl esters in a fat or oil. (2) The difference between acid number and saponification number.

"Esteron" [Dow]. TM for a series of weed- and brush-control products; they are formulated esters of 2,4-D and 2,4,5-T.

estradiol. CAS: 50-28-2. $C_{18}H_{24}O_2$. A female sex hormone. It occurs in two isomeric forms, α and β . β -estradiol has the greatest physiological activity of any naturally occurring estrogen. The α -form is relatively inactive. Commonly used preparations are the benzoate, dipropionate, and valerate, as well as ethinylestradiol.



Properties: (β -form): White or slightly yellow, small crystals or crystalline powder, odorless, mp 173-179C, stable in air. Almost insoluble in water; soluble in alcohol, acetone, dioxane, and solutions of alkali hydroxides; sparingly soluble in vegetable oils.

Derivation: Isolated from human and mare pregnancy urine, commercial synthesis from cholesterol or ergosterol.

Grade: NF (β -form).

Hazard: A carcinogen (OSHA).

Use: Medicine (estrogenic hormone).

estragole. (chavicol methyl ether; methyl chavicol). CAS: 140-67-0.